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Review Article

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Human Health and Probiotics: Present Understanding and Future Pathways

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Probiotics are live microorganisms that help the host's health when given in sufficient quantities. Because of its demonstrated and possible benefits for maintaining health and averting illness, they have become one of the most studied functional foods of the past 20 years. The word probiotic comes from the Greek meaning “for life,” highlighting their encouraging effect on human physiology. Probiotics are now commonly taken as functional drinks, nutritional supplements, or added to common meals like curd and fermenting milk products. According to the most recent scientific research, probiotics are crucial for immunity, metabolic control, mental health, and the treatment of chronic illnesses in addition to digestive health.

Keywords: Probiotics, therapeutic effect, gut, mood.

Introduction

Probiotics constitute live microorganisms (bacteria, yeast, etc.) and are beneficial for maintaining a healthy gut when consumed in appropriate amounts. Probiotics have been in use for ages, with evidence supporting their use by ancient Romans and Greeks in the form of fermented dairy produce since the onset of Middle Bronze Age (1). Advancements in the field of science have improved our knowledge with respect to the advantageous microorganisms, specifically the way these microbes influence gut health and quality of life. The World Health Organization (WHO) defines probiotics as “live microbes which confer a health benefit to their host when administered in adequate amounts” (2).

Humans are home to a great many microbes that comprise intricate ecosystems, referred to as microbiomes, in various tissues, including the alimentary canal, epidermis, oral-mucosa, and urothelium. The gut microbiota influences nutrient absorption, immune responses, cellular metabolism, and even nervous system functioning, which is why it is considered crucial in regulating human health (3).

Achieving “Gut homeostasis”, an equilibrium where the advantageous microbes supersede the potentially detrimental microbes to create an environment promoting sound health and disease control, is facilitated by Probiotics (4).

The growing attention for probiotics echoes a larger shift towards preventive medicine and naturalistic mediations. As researchers explore the intricate mechanisms substantiating gut health and overall well-being, probiotics have evolved from conventional leavening agents to advanced health supplements with implementation in various areas of medicine (5). This article assesses the recent take on the role of probiotics with respect to human health by investigating the intricate mechanisms and safety issues involved with their use, and potential applications.

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Probiotic: Sources, Forms, and Compositions

Commonly Found Probiotic Strains

Probiotic strains belonging to the *Lactobacillus* and *Bifidobacterium* genus have been in use for ages, and their safety and effectiveness has been substantiated scientifically. *Lactobacillus acidophilus, L. rhamnosus, L. casei, L. plantarum, Bifidobacterium longum,* and *B. breve* are a few of the most widely employed strains in probiotic formulations (6). Several microorganisms such as, *Bacillus, Streptococcus, Enterococcus,* and *Saccharomyces boulardii,* are also employed in probiotic formulations (7).

The inherent attributes and functionality of probiotic strains are unique, making the nutritional benefits of one strain completely different from the other strains, even when both strains belong to the same species (8). The specificity exhibited by probiotic strains is crucial in selecting the strains for specific health applications. Owing to the natural prevalence of *Lactobacillus acidophilus* in various human tissues, such as, oral mucosa, lungs, gastrointestinal tract, genitals, and urinary tract, these probiotic strains have wide applications (9).

Novel and Probiotic-Prebiotic Formulations (symbiotic)

Prebiotics are the non-digestible foods that specifically stimulate the proliferation of useful bacteria. Synbiotics, a combination of prebiotics and probiotics, improve the efficacy of probiotics to a greater extent. These combinations not only enhance the inherent viability and stability of probiotics but also inhibit the pathogens. Compounds such as oligosaccharides, fibers and various other substances found in certain foodstuffs (chicory roots, wheat, asparagus, onions, garlic, etc.) are considered prebiotics (10).

Advancements in the field of encapsulation have helped to overcome the hurdles related to designing probiotic formulations, improving shelf life, and absorption by the gastrointestinal tissues (11). Various encapsulation methods, ranging from spray drying, microencapsulation, and gel entrapment by employing different materials like CaCl2, natural biopolymers (Sodium alginate, polysaccharides), protect probiotics from unfavorable conditions (12). These methods improve the viability of probiotic formulations, enable sustained release, and minimize the losses during processing, thus encouraging the wider application of probiotics as nutraceuticals (13).

Table 1 illustrates the common microbes employed as probiotics

Table 1: Common probiotic strains and their applications

S. No	Strain	Category	Applications	References
1	*Lactobacillus acidophilus*	Bacteria	Gastrointestinal health, vulvo-vaginal microbiome, and immunological responses	8
2	*Bifidobacterium longum*	Bacteria	Anti-inflammatory activity, maintaining the intestinal-mucosa barrier	6
3	*Saccharomyces boulardii*	Yeast	Managing antimicrobial-induced diarrhea	7
4	*Lactobacillus rhamnosus GG*	Bacteria	Managing hospital-acquired diarrhea in kids	8
5	*Bifidobacterium infantis*	Bacteria	Management of Irritable bowel	6

Sources of Probiotics (Dietary and Supplementary

Fermented foodstuffs and dietary supplements are common sources of probiotics. Indigenous fermented food items such as kefir, kombucha, kimchi, and yogurt are a good source of active pools of beneficial bacteria. Though a good source, these indigenous foods lack enough concentration of probiotics in comparison to the supplements. However, these traditional foods provide greater nutritional coverage and biodiversity to the gut microbiome. Probiotics supplements are available in various forms, ranging from pills, capsules, powders, to suspensions, frequently providing highly concentrated forms of specific beneficial strains. Depending on one's health goals and therapeutic requirements, the source of the probiotics can be chosen (14).

Mechanisms Involved in Conferring Health Benefits:

Antibiotic Production and Omission-Based Competition:

Probiotic formulations aid in maintaining sound health by various mechanisms, one of the major mechanisms is "competitive exclusion". It involves competition for the available nutrients and reactive sites on the gastrointestinal tissues between probiotic microbes

and pathogens. Probiotics essentially avert the proliferation and colonization of pathogens by saturating the available attachment sites in tissues (15).

Pathogens are inhibited by the production of antimicrobial compounds by probiotic organisms. For instance, bacteriocins, volatile fatty acids (VFAs), H2O2, and diacetyl are among the antimicrobials released by probiotics (16). These biomolecules specifically alter the gut microbiome, creating a vulnerable environment for pathogens while favoring the proliferation of useful microbes. Similarly, VFAs, such as acetate and butyrate, have been known to exhibit anti-inflammatory activity and improve gut barrier function, while inhibiting pathogen colonization (17).

Improving Gut Barrier Function and Immunoregulation:

Probiotic formulations contribute to defenses against foreign elements (pathogens) by strengthening the gastrointestinal barrier. These probiotic formulations enhance the expression transmembrane and adaptor proteins that help in the establishment of a semipermeable barrier in intestinal endothelium and epithelium. This barrier maintains tissue homeostasis and prevents the movement of toxins, undigested foods and pathogens into the vascular system, a condition which is generally referred to as "leaky gut" (18).

Probiotics exhibit immunoregulatory effects and engage with gut-associated lymphoid tissue (GALT) affecting both innate and adaptive immunological responses. These formulations improve host defenses by enhancing antibody production and stimulating immune cells (19). Certain probiotics strains can trigger dendritic cell signaling and alter cytokine secretion, leading to stronger antiviral immunity and diminished inflammation (20).

Neurological and metabolic influences

Recent studies have indicated that probiotics can impact brain function via the gut-brain axis, a network that enables two-way communication between the digestive system and the central nervous system. These useful microbes may have a role in the secretion of neurotransmitters, management of neuro-inflammation, and stress induces responses, which highlights their positive effects on mental health management (21).

While considering metabolomics, probiotic formulations affect energy utilization, nutrient assimilation and insulin responsiveness. Probiotics have been found to influence secretion of secondary metabolites, regulation of bile acid metabolism and management of cholesterol levels. Notably, specific strains such as *Akkermansia muciniphila* have demonstrated potential to manage blood glucose levels and weight by enhancing production of volatile fatty acids and insulin responsiveness (22).

Medical Application: evidence-supported use of probiotic formulations

Gastrointestinal Tract Related Disorders

Probiotic formulations are most widely used and most studied in managing and preventing gastrointestinal tract disorders. Strong data supports their role in lowering the risk of antibiotic-associated diarrhea (AAD), including diarrhea caused by *Clostridiodes difficile* (23). By preserving the equilibrium of gut microbiota during the course of antibiotic treatment, probiotics can reduce the likelihood of AAD by nearly 50% as depicted in meta-analyses (24). In irritable bowel syndrome (IBS), probiotics may have a role in alleviating abdominal discomfort and other symptoms, although the search for more effective strains and formulations is still going on. In case of Inflammatory Bowel Disease, including ulcerative colitis and Crohn's disease, evidence suggests that incorporating probiotics, prebiotics or symbiotic to usual treatment strategies may induce remission especially in ulcerative colitis patients (25).

Role of Probiotics in Metabolic and Cardiovascular Health

Studies have demonstrated that probiotics play a role in improving metabolic wellbeing by managing body weight, blood sugar and lipid levels. Certain strains have been found to be effective in maintaining the body weight, insulin responsiveness, triglyceride levels and preventing hepatic steatosis in animal models exposed to high-fat-diet-induced obesity. Human-studies have demonstrated the positive role of specific probiotic formulations in lowering total and LDL blood cholesterol levels. Nonetheless, extensive research is necessary to identify the most effective strains and their recommended dosage of formulations (26).

Probiotics may offer cardiovascular benefits which might extend to systemic blood pressure management as well as endothelial function improvement apart from just regulating the blood cholesterol levels. Different mechanisms including entero-hepatic metabolism of bile salts, synthesis of biologically active proteins, anti-inflammatory action and modification of gut microbiome, are believed to be responsible for the beneficial effect of probiotics on human heath (27).

Probiotics' role in maintaining Mental Wellbeing and Neurological Activity

Researchers opined that probiotics positively impact

mental health via different signaling mechanisms such as, vagal signaling, immunological modifications, and regulating nervous -endocrine systems 'coordination (10). By lowering the inflammatory responses, managing stress-induced reactions and affecting neurotransmitter synthesis, probiotics could be employed as an effective tool in managing emotional fluctuations. The possibility of employing specific probiotic interventions to avert progression of negativity to major depressive disorder presents a new avenue in the area of psycho-dietetics (28).

Role of Probiotics in immunological reactions

Probiotics play a crucial role in regulating immunological modifications and preventing infections.

Clinical studies have established that certain probiotic strains can improve immunity against pulmonary infections. For example, *Lactobacillus helveticus* GCL1815, has been proven to effectively advert both systemic and common flu symptoms in healthy individuals by boosting antiviral immunological reactions (29). Moreover, probiotics have been used to treat and prevent a number of urogenital tract infections. Certain *Lactobacillus* strains are included in vaginal drug delivery systems to restore the modified vagina-associated microbiome during the course of antibacterial therapy. Probiotics help in maintaining a healthy vaginal environment by modifying the pH levels and preventing the pathogens from proliferating (30).

Safety Standards and Directives for the Use of Probiotics

Regulatory Guidelines and Quality Standards

The regulatory classification of Probiotics differs greatly across nations based on their designated application. For instance, in the United States, Probiotics are classified as dietary supplements, foods or medications depending on their specific use. The majority of the probiotic formulations are marketed as nutritional supplements, which do not need prior FDA approval for commercialization. This directorial system places the responsibility on manufactures to ensure the safety and packaging descriptions of the products, although they are not obligated to disclose effectiveness for particular health claims (31).

The lenient regulatory guidelines have given rise to concerns with quality standards of the probiotics being commercialized. Several studies have reported inconsistencies in the displayed nutritional content and actual nutritional profile of the marketed products. A number of discrepancies were observed even in strain labelling, its effective shelf life and even the proposed cell density present in the probiotic formulations. This lack in detailed representation and labelling about the contents of the marketed probiotics makes it difficult for the customers and medical practitioners to select suitable products. For maintaining the viability and shelf life of the probiotic formulations, it is of utmost importance to store the product under recommended conditions, but generally these storage regulations are neither followed nor communicated to the end-user of any discrepancy (32)

Safety Profiling and Vulnerable Population

Generally, probiotics are found to be safe in fit adults; however, important safety standards should be taken into account when using them in vulnerable populations. Many instances of chronic infections have been documented in preterm infants who were administered probiotic formulations; such incidents have led the U.S. Food and Drug Administration (US FDA) to caution medical practitioners about using probiotic formulations. The populations at risk include immunocompromised patients, people suffering from chronic health conditions, and individuals with conditions like endocarditis. This vulnerable group of people should be wary of using over-the-counter available probiotic formulations without consulting a professional (33).

The ability of microbial strains to cause systemic infections by diffusing or moving across the gastrointestinal barriers in compromised patients is the major risk associated with the probiotic formulations. Another concern lies in the fact that certain probiotic strains possess natural antibacterial resistance genes, and administration of probiotic formulations may lead to horizontal transfer of resistant genes to other pathogenic species. While these risks are negligible for healthy and fit adults, they might be associated with severe repercussions in vulnerable populations (31).

Practical applications of Probiotic Formulations

Medical practitioners and end-users should practice caution while selecting probiotics. Several factors, such as strain exclusivity (strains reported to exhibit intended health benefits), dosage (optimum cell density), viability (recommended storage conditions and due expiration dates), and final product efficacy (selection of certified manufacturing facility), can be considered while procuring probiotic formulations.

The administration schedule may also affect the efficiency of probiotic formulations. It has been observed that initiating probiotics consumption within two days of antibacterial therapy attenuates the antibiotic-associated diarrhea. A few of the formulations are more effective when taken along with meals, while others are more beneficial on having empty stomach. However, consistent intake of these probiotic formulations has been associated with

maintenance of general well-being (9).

New Research Avenues and Future Prospects

Customized Probiotics for targeted patients

Probiotic research is rapidly advancing towards designing customized formulations to address specific microbiota, genomic constitution, and personalized health benefits for a particular end-user. Recent developments in metagenomics, metabolomics, and bioinformatics have enhanced the competency of researchers in identifying microbial footprints linked with illness and sound health, initiating the research to develop targeted probiotic formulations.

It has been found that the particular genetic variations among individuals may influence their responses to biologically active molecules. The study of these interactions is referred to as nutrigenetics, and the way in which certain food molecules affect the genetic expression is referred to as nutrigenomics. Nutrigenetics and nutrigenomics are the major drivers in the development of next-generation targeted probiotic formulations. These strategies might help in designing customized probiotic formulations to address specific individuals' needs (8).

Applications and Innovative Probiotic Formulations

Probiotic research is expanding to new horizons in various medical fields. Current research is focused on investigating the impact of various probiotic formulations for the management of neurological disorders, autoimmune diseases, and other metabolic disorders, including cancer.

Additionally, the use of probiotics presents a potential treatment strategy, complementing conventional treatments, to manage various viral infections and other health concerns (34).

Innovative delivery methods and formulations are being curated to enhance the effectiveness of probiotics. This encompasses miniaturized capsulation techniques, synthetic probiotics (genetically modified) with improved efficacy, and symbiotic blends that are particularly designed to support the proliferation of beneficial strains. Another class of inactive microorganisms or their components, generally referred to as "postbiotics," is also gaining popularity in immunosuppressed individuals, where live probiotic formulations may pose a risk (5).

Conclusion and Futuristic Endeavors

Probiotics have come a long way from being just used as basic fermented foods to being employed as advanced therapeutics in the management of various health conditions. Present-time research endorses the use of probiotics for multiple issues such as gastrointestinal tract-related disorders, antibacterial-induced diarrhea, and irritable bowel. Recent studies indicate possible advantages associated with the use of probiotics formulations for metabolic health, mental wellness, immunity, and skin-related issues, although further research is necessary to establish stringent regulatory guidelines and standards.

Probiotics are typically beneficial for healthy individuals; however, extra care should be taken for the vulnerable population, including pre-term infants and immunosuppressed individuals. Regulatory guidelines and frameworks differ across regions, raising concerns about the reliability of product quality, which further emphasizes the need for caution while choosing a specific probiotic formulation intended for a particular use.

Though research in the field of probiotics has reached new heights, a few research gaps remain that need further exploration. Future research avenues include customized probiotic formulations to address individuals' needs, innovative formulations to improve the efficacy and shelf life of the end product, and wider application in the field of medicine. With the advancement of the knowledge pool in the field of metagenomics and metabolomics, probiotics are considered to play a significant role in preventive healthcare and holistic healthcare practices. Ongoing scientific studies into these microbes are expected to unravel the underlying mechanisms of action and their medicinal properties, further reinforcing their role in overall human well-being.

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Data Availability Declaration

Not applicable, as all the data collected are available in the public domain.

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Review Article

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Metabolic dysfunction-associated steatotic liver disease: Current perspectives

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Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), represents the most prevalent chronic liver condition worldwide. Affecting approximately one-third of the global population, MASLD is strongly associated with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), dyslipidemia, and metabolic syndrome. The renaming to MASLD underscores the central role of metabolic dysfunction in its pathogenesis and clinical spectrum. The disease ranges from simple hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Non-invasive biomarkers and imaging modalities have improved risk stratification, but liver biopsy remains the gold standard for diagnosis and staging. Current management strategies emphasize lifestyle interventions, weight loss, and cardiometabolic risk control, with emerging pharmacotherapies showing promise. MASLD poses a major burden on healthcare systems due to its progressive nature and extrahepatic associations with cardiovascular disease, chronic kidney disease, and malignancies. This review provides an updated overview of epidemiology, pathogenesis, diagnosis, management, and future directions in MASLD, highlighting evolving therapeutic opportunities and research priorities.

Keywords: Fatty liver; Liver cirrhosis; Metabolic dysfunction-associated steatotic liver disease (MASLD); Non-alcoholic fatty liver disease (NAFLD).

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic liver disorder characterized by hepatic fat accumulation in individuals with cardiometabolic risk factors in the absence of significant alcohol consumption or other secondary causes of hepatic steatosis.[1, 2] The term MASLD was recently adopted to replace the long-standing nomenclature of non-alcoholic fatty liver disease (NAFLD), in an effort to better reflect the underlying pathophysiology and reduce ambiguity in diagnosis.[3] Unlike NAFLD, the MASLD definition requires the presence of at least one metabolic risk factor, such as overweight/obesity, type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, or insulin resistance, in addition to hepatic steatosis.[4]

The spectrum of MASLD ranges from isolated hepatic steatosis, generally considered benign, to metabolic dysfunction-associated steatohepatitis (MASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).5 Importantly, liver-related morbidity and mortality correlate strongly with the stage of fibrosis rather than the presence of steatohepatitis alone.[6]

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MASLD is not confined to the liver; it is increasingly recognized as a multisystem disease linked with increased risk of cardiovascular disease (CVD), chronic kidney disease (CKD), extrahepatic malignancies, and overall mortality.[7,8] With a global prevalence approaching one-third of the adult population and rising incidence in children, MASLD has become a major public health and economic burden.[9]

Epidemiology and Global Burden

MASLD is the most prevalent chronic liver disease worldwide, affecting approximately 25–30% of the global adult population.[10] Its prevalence parallels the increasing rates of obesity, T2DM, and sedentary lifestyles. Regional variation exists: the highest prevalence is reported in the Middle East and South America (30–35%), while lower prevalence is observed in sub-Saharan Africa (13–18%).[11] In Asia, prevalence has risen sharply over the last two decades, reflecting dietary westernization and urbanization.[12]

MASLD is strongly associated with obesity, with up to 70–90% of obese individuals demonstrating hepatic steatosis on imaging.[13] Among patients with T2DM, prevalence exceeds 50%, with advanced fibrosis present in 15–20%.[14] Importantly, MASLD also occurs in lean individuals, particularly in Asian populations, underscoring the role of genetic and environmental factors.[15]

Pediatric MASLD is increasingly recognized, with global prevalence estimated at 7–10% among children and up to 30–40% in obese adolescents.[16] Early onset MASLD may progress more rapidly, increasing lifetime risk of cirrhosis and HCC.

The disease imposes a substantial healthcare and economic burden. In the United States alone, MASLD-related healthcare costs are projected to exceed $100 billion annually.[17] Moreover, MASLD is now a leading indication for liver transplantation in Western countries, surpassing viral hepatitis.[18]

Pathogenesis and Risk Factors

The pathogenesis of MASLD is multifactorial, involving a complex interplay between genetic, metabolic, environmental, and gut microbiome-related factors.

Insulin Resistance and Lipotoxicity

Insulin resistance is central to disease development. Impaired insulin signaling leads to increased lipolysis, elevated free fatty acid flux to the liver, and de novo lipogenesis.[19] Excess lipid accumulation induces lipotoxicity, mitochondrial dysfunction, oxidative stress, and hepatocellular injury, promoting inflammation and fibrosis.

Genetic Susceptibility

Genome-wide association studies have identified key genetic variants influencing susceptibility and disease progression. The **PNPLA3 I148M** polymorphism is strongly associated with hepatic fat accumulation and fibrosis progression.[20] Other variants, including **TM6SF2, MBOAT7, and HSD17B13**, modulate risk and clinical phenotype.[21]

Gut Microbiota and Intestinal Permeability

Dysbiosis of gut microbiota contributes to disease pathogenesis through increased intestinal permeability, endotoxin release, and activation of hepatic inflammatory pathways.[22] Microbiome-derived metabolites, such as short-chain fatty acids and bile acid derivatives, further influence hepatic lipid metabolism.

Dietary and Lifestyle Factors

Western-style diets rich in fructose, saturated fat, and processed foods promote hepatic fat deposition and inflammation.[23] Sedentary lifestyle exacerbates insulin resistance and metabolic dysfunction, while physical activity confers protective effects.

Additional Risk Factors

Other contributors include endocrine disorders (e.g., polycystic ovary syndrome, hypothyroidism), obstructive sleep apnea, and certain medications such as corticosteroids and amiodarone.[24]

Clinical Spectrum

MASLD encompasses a wide histological and clinical spectrum:

Simple Steatosis (MASLD without MASH): Characterized by hepatic fat accumulation without significant inflammation or fibrosis; generally benign with low risk of progression.[25]

MASH: Defined by steatosis, lobular inflammation, and ballooning degeneration; carries higher risk of fibrosis and adverse outcomes.[26]

Fibrosis and Cirrhosis: Progressive fibrosis can culminate in cirrhosis, portal hypertension, and liver failure. Fibrosis stage is the most important predictor of liver-related outcomes.[27]

Hepatocellular Carcinoma: MASLD-related cirrhosis increases HCC risk, but HCC can also develop in non-cirrhotic MASLD, complicating surveillance strategies.[28]

Extrahepatic Manifestations: Cardiovascular disease, CKD, and certain malignancies (colorectal, breast) are major causes of mortality in MASLD patients.[29]

Diagnosis

Accurate diagnosis and staging are critical for prognosis and management.

Clinical and Laboratory Evaluation

Diagnosis requires evidence of hepatic steatosis in the presence of metabolic dysfunction and exclusion of secondary causes (significant alcohol intake, viral hepatitis, Wilson's disease, etc.).[5] Liver enzymes may be normal in many patients, limiting their utility.

Imaging Modalities

Ultrasound: Widely available and inexpensive, but limited sensitivity in detecting mild steatosis or differentiating fibrosis stages.

Controlled Attenuation Parameter (CAP, FibroScan): Provides quantitative assessment of steatosis and simultaneous fibrosis measurement using transient elastography.[30]

Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF): Highly accurate for quantifying hepatic fat content; increasingly used in clinical trials.

MR Elastograp hy: Superior accuracy for fibrosis staging compared to other non-invasive modalities.[31]

Non-Invasive Biomarkers

Several scoring systems aid in fibrosis risk stratification, including the **Fibrosis-4 (FIB-4) index** and **NAFLD fibrosis score (NFS).**[32] Serum biomarkers such as cytokeratin-18 fragments and novel fibrosis panels are under investigation.

Liver Biopsy

Despite limitations, biopsy remains the reference standard for diagnosing MASH and staging fibrosis. However, its invasiveness, cost, and sampling variability restrict routine use.[33]

Management

Currently, no approved pharmacological therapy exists for MASLD. Management is centered on treating the underlying metabolic drivers (weight, insulin resistance, dyslipidaemia) and on preventing progression to fibrosis and cirrhosis. Current guidance emphasizes lifestyle intervention as first-line therapy, with pharmacologic and procedural treatments reserved for selected patients with advanced disease or when lifestyle measures fail.[34, 35]

Goals of therapy

Primary goals are: (1) reduce liver fat and hepatic inflammation (MASH), (2) halt or reverse fibrosis progression, and (3) treat cardiometabolic comorbidities to reduce overall morbidity and mortality. Management must be individualized by fibrosis stage and cardiometabolic risk.[34]

Lifestyle interventions (cornerstone)

Lifestyle change remains the foundation of MASLD treatment. Structured programs that produce sustained weight loss result in improvements in hepatic steatosis, necroinflammation and—when weight loss ≥7–10% is achieved—histologic improvement in

MASH and fibrosis regression in some patients.[35, 36]

Practical recommendations

Weight loss target: Aim for 7–10% body weight loss to improve steatosis and MASH; greater loss provides greater benefit.[34, 35]

Diet: Calorie reduction with emphasis on Mediterranean-style dietary patterns (high in vegetables, whole grains, lean protein; low in refined sugars and saturated fats) is supported by guidelines and trials.[35, 37]

Physical activity: At least 150–200 minutes/week of moderate aerobic exercise plus resistance training as tolerated.[35]

Alcohol: Minimize or avoid alcohol; even modest intake may worsen outcomes in some patients with MASLD.[36]

Pharmacologic approaches

No single "universal" drug is recommended for all patients with MASLD; therapy is selected by disease severity (especially presence of MASH with fibrosis) and comorbidities. Recent guideline panels and trials have updated recommendations and expanded available options.[34-36]

1. *Treat cardiometabolic comorbidities*
Pioglitazone: For biopsy-proven MASH, pioglitazone has shown histologic benefit (improved steatosis and inflammation) in multiple trials (useful in patients with and without diabetes, but consider weight gain and fracture risk).[34, 35]
Statins: Safe in MASLD and recommended for atherosclerotic cardiovascular risk management; they do not worsen liver disease and are indicated when cardiovascular indications exist.[34]

Vitamin E: Demonstrated histological benefit in non-diabetic patients with MASH, though long-term risks (prostate cancer, hemorrhagic stroke) limit use.[38]

Sodium-glucose transport protein 2 (SGLT2) inhibitors: Improve hepatic steatosis and metabolic parameters, though histological benefits require further validation.[39]

2. *Glucagon-like peptide-1(GLP-1) receptor agonists and dual incretin agonists*
GLP-1 receptor agonists (semaglutide) and dual Glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 agonists (tirzepatide) produce substantial weight loss and reduce liver fat; trials suggest marked improvements in steatosis and metabolic parameters, with promising signals for inflammation resolution in some studies.[35, 37]

3. *Agents targeting NASH/MASH biology*
Resmetirom (thyroid hormone receptor-β agonist): Developed specifically for MASH; recent regulatory decisions reflect evidence for liver-fat reduction and some histologic benefit in phase 3 programs.[40-42]

Other agents: under investigation or with mixed results include fibroblast growth factor analogues, farnesoid X receptor (FXR) agonists (obeticholic acid), peroxisome proliferator-activated receptor (PPAR) agonists, and combination strategies.[34, 41-44]

4. *When to consider pharmacotherapy for the liver itself*
Most guidance recommends considering MASH-directed pharmacotherapy for patients with biopsy-proven MASH and ≥F2 fibrosis or at high risk of progression, particularly if lifestyle interventions have failed.[34, 42]

Bariatric/metabolic surgery and endoscopic options

For patients with obesity and MASLD, bariatric/metabolic surgery (e.g., sleeve gastrectomy, Roux-en-Y gastric bypass) is highly effective at substantial and durable weight loss and often results in resolution or marked improvement of steatosis and MASH; it is appropriate when surgical criteria for obesity are met. Endoscopic weight loss procedures are emerging options with promising effects.[35, 36]

Monitoring and follow-up

Fibrosis assessment using noninvasive tests (transient elastography, serum fibrosis scores like FIB-4 or NAFLD Fibrosis Score) is essential to

stratify risk and guide therapy intensity. Repeat assessment depends on baseline fibrosis and interventions instituted.[45]

Practical algorithm

1. Screen for metabolic drivers and assess fibrosis stage.[34]
2. Implement structured lifestyle program with weight loss target 7–10%.[35]
3. Treat cardiovascular risk factors (statins, antihypertensives, diabetes therapy).[34]
4. For biopsy-proven MASH with ≥F2 fibrosis: discuss pharmacologic options and trials.[43]
5. For eligible patients with obesity and MASLD: consider bariatric/metabolic surgery.[35]

Nomenclature changes (NAFLD→MASLD) refocus attention on systemic metabolic drivers. Combination therapies (antifibrotic + metabolic) and precision-medicine approaches are in development.[36, 37, 41]
Lifestyle modification with meaningful, sustained weight loss remains the bedrock of MASLD therapy. Pharmacotherapies (e.g., GLP-1/GIP agonists, resmetirom) offer options for selected patients. Management should be individualized, fibrosis-directed, and integrated with cardiometabolic care.[34-36]

Special Populations

Pediatric MASLD

Early detection and lifestyle interventions are critical. Pediatric MASLD may have distinct histological patterns and more aggressive progression.[46]

Lean MASLD

Particularly prevalent in Asia, lean MASLD highlights the contribution of genetic susceptibility and visceral adiposity. Despite normal body mass index (BMI), these patients remain at risk for fibrosis and cardiometabolic complications.[47]

Elderly Patients

MASLD in the elderly is often underdiagnosed due to normal liver enzymes and overlapping comorbidities. Age-related sarcopenia exacerbates disease progression.[48]

Future Directions and Research Gaps

Despite advances, MASLD remains underdiagnosed and undertreated. Key challenges include development of reliable non-invasive biomarkers for steatohepatitis and fibrosis staging, identification of effective, safe, and widely accessible pharmacological therapies, and tailored management approaches for pediatric, lean, and elderly populations. Integration of digital health tools and artificial intelligence in risk stratification and surveillance is needed, besides understanding the long-term safety and efficacy of emerging agents in real-world settings.

Conclusion

MASLD has emerged as a leading cause of chronic liver disease, tightly linked with the global epidemics of obesity and metabolic syndrome. Its multisystem nature, rising prevalence, and association with adverse hepatic and extrahepatic outcomes make it a critical public health challenge. While lifestyle modification remains the cornerstone of management, promising pharmacotherapies are on the horizon. Continued research into disease mechanisms, diagnostic modalities, and therapeutic interventions is essential to reduce the growing burden of MASLD.

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Review Article

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Pigmented Rice: From Nutritional Richness to Therapeutic Application

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Pigmented rice varieties, such as black, red, and purple, have gained increasing attention for their high content of bioactive compounds and nutritional value. Unlike white rice, these colored grains retain their bran layers, which are rich in anthocyanins, phenolic acids, flavonoids, ϒ -Oryzanol, dietary fiber, and essential minerals. These compounds contribute to various health-supporting properties including antioxidant, anti-inflammatory, and glycemic regulation potential. This review presents recent findings on functional relevance of pigmented rice, highlighting its role in health-oriented food development. In addition to their nutritional advantages, pigmented rice varieties support clean label formulations and provide natural color enhancement in food products. However, factors such as processing-related degradation, consumer acceptance, and lower yield compared to white rice continues to pose challenges

Keywords: Pigmented rice, therapeutic potential, functional food

Introduction

Pigmented rice refers to landraces and improved cultivars of Oryza sativa L. whose bran layers contain red, purple, or black pigments formed during grain filling. These colors arise from the synthesis and deposition of flavonoid pigments principally anthocyanins and pro-anthocyanidins while the grain develops in warm, waterlogged paddies typical of south-east and north-east Asian agro-ecosystems [1]. Black 'Chak-hao' from Manipur (India), red 'Comargue' from France and purple 'Khao Kum' from Thailand, germinate and grow under the same flooded-field conditions as white rice but retain their colored bran because the outer layers are left intact after milling [2,3]. Their long history in traditional medicine, coupled with modern interest in clean-label ingredients, has moved pigmented rice steadily from regional staple towards the global function-food arena [4]. This review aims to explore the health promoting properties of pigmented rice varieties including black, red, and purple rice with a focus on their potential as functional food ingredients.

Health benefits of pigmented rice

Varieties of pigmented rice are abundant in bioactive compounds, especially anthocyanins flavonoids, phenolic acids, and γ-oryzanol. These compounds contribute significantly to the antioxidant and anti-inflammatory properties of pigmented rice.

The high anthocyanin content, especially in black and purple rice, plays crucial role in the elimination of free radicals, thereby lowering the impact of oxidative stress. These antioxidants help in protecting the cellular components by protecting cells from the effects of ROS-related damage, which are known to contribute to aging and chronic health issues, particularly those affecting the heart, neuro degeneration, and cancer [13]. Among pigmented rice types, black and purple rice are especially rich in anthocyanins, which are powerful antioxidants.

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Table 1: Summarizing notable commercial pigmented rice varieties, their origin, pigment types, and key genetic traits.

Variety Name	Origin/ Group	Pigment Type	Key Genetic Traits	Nutritional Highlights	References
Cempo lreng	Indonesia, Geng-japonica	Black (anthocyanin-rich)	Possesses anthocyanin pathway genes experimental CRISPR-Cas9 knockouts of flowering repressors (Hd2, Hd4, Hd5) yield earlier maturity	High in aromatic secondary metabolites, anthocyanins, minerals	**[5]**
Kasalath	India/Japan (Indica)	Red (proanthocyanidin)	Rc (BHLH transcriptase factor on chr.7) Rd (dihydroflavonol 4-reductase on chr. 1) produce red pericrap	Rich in iron, zinc, phenolics	**[6]**
Koshihikari	Japan (Japonica)	White (non-pigmented)	Mutant Rc allele lacks pericrap color	Good source of thiamine and manganese	**[7]**
Oryza glaberrima	West Africa	Red	Wild type Rc preicrap, unique Rc-Gl mutation in white variants	Rich in iron, fiber	**[8]**
Chinese black Rice (Heirloom types e.g., 'Heixiangnuo')	China (Geng-japonica, Xian-indica	Black (anthocyanin-rich)	Anthocyanin biosynthesis genes (MYB/BHLH/WD40; QTLs identified on chr. 1,3,4,7,8,10,11)	High in anthocyanin/antioxidant potential	**[9]**
Indian red rice (traditional landraces like 'Matta' 'Rakthashali')	India (Indica, Aus)	Red	Rc and Rd genes for red color; genetic diversity present within traditional landraces	High iron, zinc, phenolics	**[10]**
Thai Hom Mali black rice	Thailand (indica)	Black (anthocyanin-rich)	Kala 4 gene (activator of anthocyanin biosynthesis), plus MYB and other regulatory loci	High in anthocyanin, vitamins	**[9]**
Black Indonesian rice	Indonesia (Circum-Aus)	Black	QTLs and SNPs associated with pericrap pigmentation and antioxidant traits	High in minerals, antioxidants	**[11]**
Red basmati	South Asia (cricum-basmati)	Red	Rc with functional alleles for red pigmentation	High in pro-anthocyanidin, aromatic compounds	**[12]**

Health benefits of pigmented rice

Varieties of pigmented rice are abundant in bioactive compounds, especially anthocyanins flavonoids, phenolic acids, and γ-oryzanol. These compounds contribute significantly to the antioxidant and anti-inflammatory properties of pigmented rice**.** The high anthocyanin content, especially in black and purple rice, plays crucial role in the elimination of free radicals, thereby lowering the impact of oxidative stress. These antioxidants help in protecting the cellular components by protecting cells from the effects of ROS-related damage, which are known to contribute to aging and chronic health issues, particularly those affecting the heart, neuro degeneration, and cancer **[13].** Among pigmented rice types, black and purple rice are especially rich in anthocyanins, which are powerful antioxidants.

Apart from antioxidants, pigmented rice also shows anti-inflammatory effects. Research has found that extracts from these rice types can lower the activity of certain inflammation-related substances in the body, like TNF-α and IL-6 **[14].** These effects are believed to come from the way rice compounds influence key pathways that control inflammation, such as NF-κB. Including pigmented rice in the diet may therefore help protect against chronic inflammation and support better health. These compounds are also known to offer anti-diabetic benefits, making pigmented rice a promising functional food**.** Pigmented rice can help manage blood sugar levels through several mechanisms. It slows down carbohydrate digestion and glucose absorption due to the presence of fiber and polyphenols, resulting in a lower glycemic response **[15].** Additionally, anthocyanins from pigmented rice have been shown to improve insulin sensitivity and reduce inflammation in tissues involved in glucose metabolism **[16].** Some in vitro and animal studies also report that pigmented rice extracts can inhibit key enzymes like α-amylase and α-glucosidase, which are responsible for breaking down complex carbohydrates into glucose **[17].**

Regular consumption of pigmented rice may therefore help in the prevention and management of type 2 diabetes, while also protecting cells from oxidative damage **[18].**

The cardio protective nature of pigmented rice is linked to its effectiveness in relieving oxidative stress, lessening inflammatory responses, and modulating blood lipid levels.

Scientific investigations suggest that consistent intake of pigmented rice may lower LDL (low-density lipoprotein) cholesterol, boost HDL (high-density lipoprotein) cholesterol, and decrease triglyceride values.

These enhancements play a role in reducing susceptibility to atherosclerotic conditions and elevated blood pressure **[19].** Notably, anthocyanins are known to strengthen vascular health, regulate blood pressure, and enhance overall circulatory performance **[20].** In terms of weight management, pigmented rice offers several advantages over white rice. It has a lower glycemic index, which means it causes a slower and more stable rise in blood sugar after eating. This helps reduce hunger and prevents overeating. Additionally, its high fiber content increases satiety, which can support healthy weight control. Some studies also suggest that pigmented rice may reduce fat accumulation by influencing fat metabolism and improving insulin sensitivity. Including pigmented rice in a balanced diet may therefore support both heart health and healthy weight maintenance, especially when combined with an overall healthy lifestyle **[21].**

Colored rice types, including crimson, deep black and violet-toned grains, are abundant in health-promoting constituents such as anthocyanins, proanthocyanins, phenolic compounds, plant-based flavonoids, and γ-oryzanol, which have shown significant potential in inhibiting cancer development. These compounds exhibit strong antioxidant activity, which helps to neutralize free radicals and reduce oxidative stress, a known factor in the initiation and progression of cancer **[18].** Among these, anthocyanins, responsible for the red to purple pigmentation, are particularly important. Studies have demonstrated that anthocyanin antioxidant-potential, which assists in counteracting free radicals and diminishing oxidative damage, is a recognized contributor in the onset and advancement of malignant conditions, without harming normal cells **[22].** They also inhibit cancer cell proliferation, angiogenesis, and metastasis **[23].** In addition, ferulic acid and phytic acid, present in pigmented rice bran, are known to suppress carcinogenesis by modulating gene expression, reducing inflammation, and improving detoxification enzyme activities. The synergistic effect of these phytochemicals may contribute to a protective role against carcinogen-induced DNA damage and inflammation-mediated tumor promotion **[24].**

Table 2: Therapeutic evidence from recent studies

Discovery/Health effect	Functional component	Target health outcome	Model	Reference
Black rice bran reduces hyperlipidaemia, fatty liver (hepatic steatosis), and oxidative stress in obese mice	Anthocyanins, fibre, SCFA modulators	Lipid profile, liver function, oxidative stress	Mouse (in vivo)	**[25]**
12-week human clinical trial showed fat loss in obese postmenopausal women with anthocyanin supplementation	Purified black rice anthocyanins	Obesity and fat mass reduction	Human (clinical)	**[26]**
Systematic review of 17 RCTs: Chronic intake of pigmented rice lowers fasting glucose, body weight, and DBP.	Whole-grain polyphenols, complex carbs	Cardio metabolic risk factors	Human	**[27]**
Acute pigmented-rice meals reduce post-prandial glycaemia and insulin, anaemia hypertension activity.	Anthocyanins. Low GI Starch, polyphenols	Glycemic control (short term)	Human(clinical)	**[27]**
Supplemented pigmented rice shows ACE inhibition (anti hypertension activity.	Rice bran, protein hydrolysates, peptides	Blood pressure regulation	In vitro	**[22]**

Table 3: Functional foods made from pigmented rice and their health effects

Functional food product	Pigmented rice used	Reported functional benefit	Reference
Rice berry yogurt	Black-purple rice	Reduced postprandial glucose and increased antioxidant capacity	**[28]**
100% black rice crackers (gluten-free)	Whole black rice flour	+37% fibre, +58% polyphenols, +95% proanthocyanidins; post-prandial glycaemia <30mg dl	**[29]**
Anthocyanin-fortified Bread	Black rice extract	Inhibited lipases, reduced starch digestibility and postprandial glycaemia and lipaemia	**[30]**
Black rice beverage	Black rice Anthocyanin extract	Improved post-meal glycemic and lipid profiles in overweight /obese adults	**[31]**
Germinated & roasted red rice	Red rice	Increased total phenolic, flavonoids, and antioxidant activity (DPPH, ABTS); safe microbiologically	**[32]**
Functional idli with pigmented rice	Black & red rice	Improved nutritional and sensory quality compared to white rice	**[33]**
Pigmented rice flour muffins/ cakes	Mixed pigmented rice Red black brown	Higher total phenolic and flavonoid content, healthy snacking option	**[34]**
Pigmented brown rice flour	Brown rice	Exhibited high water/oil absorption, antioxidant activity, suitable for gluten free or health-oriented food products	**[35]**

Limitation and consideration

Despite its strong nutritional and therapeutic potential, wider adoption of pigmented rice in functional food systems faces key challenges. Anthocyanins and other bioactives are unstable and can lose 30–50% of their content during cooking and processing, reducing antioxidant activity **[36, 32].** Agronomically, most pigmented cultivars are traditional, lower-yielding, and slower-growing than commercial white hybrids, making them less viable for large-scale farming without supportive policy or premium pricing, while susceptibility to stress adds further constraints **[3, 37].** Consumer acceptance is another barrier, as the dark color and bitter or nutty taste can deter those accustomed to white rice, with sensory studies showing lower overall acceptability outside health-conscious groups **[29].** Clinical evidence, though promising, remains limited in scale, duration, and population diversity, restricting broad health claims **[27].** Post-harvest practices like de-husking and minimal polishing must be optimized to retain functional compounds, and emerging approaches such as encapsulation, co-pigmentation, and fermentation could improve anthocyanin stability and bioavailability, though scalable solutions are still under research **[22].** Overall, unlocking the potential of pigmented rice requires coordinated agronomic, technological, economic, and sensory innovations supported by interdisciplinary research and policy.

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Original Article

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Factors associated with the development and outcome of acute respiratory distress syndrome: A prospective observational study

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Background: Acute respiratory distress syndrome (ARDS) is a life-threatening disorder of the lungs associated with high mortality. This work was done to determine the risk factors for the development of ARDS and the predictors of adverse clinical outcomes in patients with ARDS.

Methods: This hospital-based prospective observational study included 96 patients who fulfilled Berlin's criteria for ARDS. Their demographic, vital, and biochemical parameters were recorded and the etiology of ARDS in each patient was determined along with the severity of the disease and corroborated with the survival and outcome of patients.

Results: Male predominance was observed (62.5%). Sepsis (45.8%) was overall the most common cause while pneumonia (41.6%) was the most common direct cause of ARDS. Abdominal pain, altered sensorium, and low mean arterial pressure (MAP) were associated with poor outcomes ($p < 0.05$ each). Increased mortality was associated with low hemoglobin ($p = 0.004$), low hematocrit ($p = 0.015$), thrombocytopenia ($p = 0.021$), raised serum creatinine ($p = 0.047$), hyperbilirubinemia ($p = 0.020$), raised serum alkaline phosphatase ($p = 0.011$), hypoalbuminemia ($p < 0.001$), raised d- dimer ($p = 0.011$), and high illness severity scores like sequential organ failure assessment (SOFA) score ($p = 0.004$) and acute physiology and chronic health evaluation (APACHE) score ($p = 0.002$). The mortality rate of ARDS was 58.3%.

Conclusions: Sepsis and pneumonia are the most frequent causes of ARDS associated with high mortality. The presence of abnormal clinical and biochemical parameters has a significant effect on the outcome of patients with ARDS.

Keywords:

Acute respiratory distress syndrome; Predictors; Development; Clinical outcome; SOFA score;

Introduction

Acute respiratory distress syndrome (ARDS) is a disorder of diverse etiologies described as a consistent, recognizable pattern of injury of the lung which causes an acutely devastating form of inflammatory lung injury with a high mortality rate in a short period of time and remarkable long-term morbidity among survivors[1].

ARDS is associated with acute onset of hypoxemia i.e., within 7 days of known clinical insult with bilateral lung infiltrates seen on chest skiagram, that occurs due to the injury to the parenchyma of lungs causing alveolar epithelial injury or injury to pulmonary vasculature causing lung endothelial injury[2-4] The incidence of ARDS varies from region to region, which ranges from 1.5 to 79 cases of ARDS per lakh population. Studies in the Indian population report an incidence rate of 11.4% among ventilated patients.5-8

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Mortality due to ARDS remains high and depends on the region, intensive care unit (ICU) type, etiology, ARDS definition, etc. With an increase in severity of ARDS, the mortality increases from 27% to 45%.9-12 The mortality rate of the Indian population in western and northern regions is 57%13 and 47.8%14, respectively.

There are approximately 60 known causes of acute respiratory distress syndrome. The causes of ARDS are divided into direct or indirect, also known as pulmonary or extra-pulmonary. Both medical and surgical causes contribute to ARDS. Common causes include direct causes such as pneumonia, inhalational injury, gastric contents aspiration, and drowning, and indirect causes like pancreatitis, sepsis, non-cardiogenic shock, severe burns, major trauma, and multiple transfusions. Among the direct causes of ARDS, aspiration, pneumonia, and infections are predominantly seen, while systemic sepsis remains the primary indirect cause of acute respiratory distress syndrome.13, 15-17

Risk factors such as advanced age, partial pressure of arterial oxygen (PaO2)/ fraction of inspired oxygen (FiO2) or PF ratio, oxygenation index, need for mechanical ventilation, development of non-pulmonary organ dysfunction such as liver cirrhosis, hypoalbuminemia, presence of pulmonary ARDS, length of hospital stay, and severity illness scores such as acute physiology and chronic health evaluation (APACHE) score and severity scores like sequential organ failure assessment (SOFA) score are the predictors of mortality in ARDS patients.18, 19

This study aimed to analyze the factors associated with the development and outcome of ARDS of varying etiologies.

Materials and methods

This prospective observational study was conducted in a tertiary care institute in Uttarakhand, India from July 2021 to June 2022. The study was approved by the institutional ethics committee and was in accordance with the principles of the Declaration of Helsinki. Patients with ARDS were included in the study after obtaining informed written consent from the patients or next of kin if a patient was not able to give consent due to severe illness.

The study included 96 patients above the age of 18 years who fulfilled Berlin's criteria for ARDS which include, acute onset within 7 days of a clinical insult by known risk factor or new or aggravating symptoms, chest radiograph suggestive of bilateral infiltrates which is not completely explained by pleural effusion, lung collapse or pulmonary nodules, hypoxemic respiratory failure not explained by heart failure and fluid overload, and PF ratio ≤300 with a continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) value of minimum 5 cm of water.5, 20

Parameters such as demographic profile (age and gender), clinical manifestations, co-morbidities, vital parameters [including temperature, pulse, heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)], the need of vasopressor, the severity of ARDS based on PF ratio, baseline laboratory parameters, ventilation requirement (invasive/non-invasive), and length of hospital stay were documented. Illness severity scores such as APACHE score and SOFA score were recorded within 24 hours of hospital admission.

The etiology of ARDS was determined based on clinical manifestations, physical examination findings, radiographic assessment, and appropriate biochemical and microbiological investigations. The etiology of ARDS was classified as direct or pulmonary and indirect or extra-pulmonary.

Patients were assessed twice during the hospitalization-first at the time of admission and again at the time of discharge or at the time of death. The patients were categorized into two groups, in which those patients who completely recovered and were discharged were considered as the survivor group and those patients who did not recover or died or were discharged against medical advice were included in the non-survivor group.

Data Management and Statistical Analysis

Results were analyzed by using SPSS Software version 22. The one-sample Kolmogorov-Smirnov test was employed to determine whether the data sets differed from a normal distribution. Student's unpaired t-test was applied for comparing the normally distributed quantitative data between the two groups, whereas, non-normally distributed data were analyzed using the Mann-Whitney U test. The Chi-square test was used for testing differences between proportions or associations between various variables. A p-value < 0.05 was taken as statistically significant.

Results

Out of 96 patients, 42 (43.7%) patients were above the age of 60 years. Among patients who did not recover, a maximum (28.6%) were from the age group of 61 to 70 years. No significant association was seen between the age of patients and the outcome of ARDS ($p = 0.680$). The majority of patients were male, with a male-to-female ratio of 1.6:1. Mortality was observed among 35 (62.5%) males and 21 (37.5%) females. No significant association was seen between gender and the outcome of patients with ARDS ($p = 0.823$).

Sepsis was overall the most common cause of ARDS while pneumonia was the most common direct cause of ARDS. Among patients who survived, pneumonia, sepsis, and pancreatitis were present in 27.5%, 25%, and 12.5% of patients respectively. Among patients who did not survive, sepsis, pneumonia, pancreatitis, and aspiration were present in 60.7%, 51.7%, 7.1%,

and 5.3% of patients respectively. Pneumonia and sepsis had a significant association with the outcome (p = 0.029 and 0.002 respectively). Comorbidities were present in 75% of survivors and 66% of non-survivors. Hypertension (32.2%) and type 2 diabetes mellitus (29.1%) were the most common comorbidities, followed by chronic obstructive pulmonary disease (COPD) (15.6%) and chronic kidney disease (CKD) (10.4%) (Table 1).

Table 1: Demographic profile, etiology, and co-morbidities of ARDS survivors and non-survivors

Parameters	Number of patients (%)		p-value
	Survivors (n=40)	Non-survivors (n=56)	
Demographic profile			
Age			
<60 years	21 (52.5)	33 (58.9)	0.680
>60 years	19 (47.5)	23 (41.0)	
Gender			
Males	25 (62.5)	35 (62.5)	0.823
Females	15 (37.5)	21 (37.5)	
Environmental factors			
Smoking			
Yes	21 (52.5)	31 (55.3)	1
No	19 (47.5)	25 (44.6)	
Alcohol use			
Yes	16 (40)	23 (41.0)	0.920
No	24 (60)	33 (58.9)	
Etiology of ARDS			
Pulmonary			
Pneumonia	11 (27.5)	29 (51.7)	0.029
Aspiration	0 (0)	3 (5.3)	0.263
Non-pulmonary			
Sepsis	10 (25)	34 (60.7)	0.002
Pancreatitis	5 (12.5)	4 (7.1)	0.483
Comorbidities			
Chronic kidney disease	2 (5)	8 (14.2)	0.185
Chronic obstructive pulmonary disease	8 (20)	7 (12.5)	0.475
Type 2 diabetes mellitus	11 (27.5)	17 (30.3)	0.920
Hypertension	15 (37.5)	16 (28.5)	0.483
Coronary artery disease	7 (17.5)	0 (0)	0.001
Chronic liver disease	0 (0)	6 (10.7)	0.078
Cerebrovascular accident	1 (2.5)	5 (8.9)	0.395
Pulmonary tuberculosis	2 (5)	1 (1.7)	0.568
Malignancy	2 (5)	1 (1.7)	0.568
Rheumatoid arthritis	0 (0)	3 (5.3)	0.263
Hypothyroidism	1 (2.5)	0 (0)	0.416
Gout	1 (2.5)	0 (0)	0.416
Obstructive sleep apnea	1 (2.5)	0 (0)	0.416
Post renal transplant	0 (0)	1 (1.7)	1
Hepatitis C	0 (0)	1 (1.7)	1

The most common clinical manifestations were shortness of breath (55.2%), fever (39.5%), altered sensorium (23.9%), abdominal pain (21.8%), vomiting (18.7%), and cough (16.6%). Abdominal pain and altered sensorium were present in a significantly higher number of patients among non-survivors than survivors (p = 0.023 and p < 0.001 respectively). The mean arterial pressure (MAP) was significantly lower among non-survivors than survivors (p = 0.049). Vasopressors were needed in 32.5% of survivors and 46.4% of non-survivors. The association between the need for vasopressor support and outcome was statistically not significant (p = 0.247).

The majority of patients had mild (43.7%) to moderate (39.5%) severity of ARDS. Among non-survivors, 21.4% of patients had severe ARDS followed by moderate (41%) and mild (37.5%) forms of ARDS. No significant association was seen between the severity of ARDS and mortality (p = 0.212). Mechanical ventilation was required in 82.5% of survivors and 94.6% of non-survivors. The association between the requirement for ventilation and the outcome was found to be statistically not significant (p = 0.087) (Table 2).

Table 2. Clinical parameters of ARDS survivors and non-survivors

Parameters	Number of patients (%)		p-value
	Survivors (n=40)	Non-survivors (n=56)	
Clinical manifestations			
Fever	14 (35)	24 (42.8)	0.571
Shortness of breath	21 (52.5)	32 (57.1)	0.806
Sore throat	6 (15)	2 (3.5)	0.063
Cough	10 (25)	6 (10.7)	0.115
Hemoptysis	0 (0)	1 (1.7)	1
Chest pain	4 (10)	2 (3.5)	0.395
Vomiting	6 (15)	12 (21.4)	0.596
Nausea	3 (7.5)	3 (5.3)	0.999
Loss of appetite	3 (7.5)	2 (3.5)	0.646
Abdominal pain	4 (10)	17 (30.3)	0.023
Altered sensorium	2 (5)	21 (37.5)	< 0.001
Mean arterial pressure (mmHg)*	88.27 ± 24.41	78.62 ± 22.77	0.049
Vasopressor requirement			
Yes	13 (32.5)	26 (46.4)	0.247
No	27 (67.5)	30 (53.5)	
Severity			
Mild[a]	21 (52.5)	21 (37.5)	
Moderate[b]	15 (37.5)	23 (41.07)	0.212
Severe[c]	4 (10)	12 (21.4)	
Ventilation requirement			
Yes	33 (82.5)	53 (94.6)	0.087
No	7 (17.5)	3 (5.3)	

*Data represent mean ± SD; [a]Mild: PaO_2/FiO_2 (PF) ratio 201-300 mm Hg; [b]Moderate: PF ratio 101-200 mm Hg; [c]Severe: PF ratio ≤ 100 mm Hg, based on the lowest PF ratio available on the day of ARDS diagnosis.

Among biochemical variables, hemoglobin, hematocrit, platelet count and serum albumin were significantly lower while serum creatinine, total bilirubin, alkaline phosphatase (ALP), and D-dimer were significantly higher among non-survivors than survivors (p < 0.05 each). Initial SOFA score and APACHE score were significantly higher among non-survivors compared to survivors. The associations between severity illness score such as SOFA score (p = 0.004) and APACHE score (p = 0.002) and outcome were found to be statistically significant (Table 3).

Discussion

In our study, 43.7% of patients were the above age of 60 years. In many studies, advanced age or age above 60 years is an independent predictor of mortality.1, 21 In a study done by Rashid et al.,22 the mean age of recovered patients was significantly lower than the mean age of patients who died (44.41± 14.53 years vs 49.08 ± 16.57 years). In a study of an elderly population of age more than 65 years, Sehgal et al.23 observed that mortality was lower in the elderly population, while we observed that no significant difference existed between the mean age of survivors and non-survivors (57.50 ± 13.72 years vs. 54.66 ± 14.91 years).

In our study, out of 96 patients, 62.5% were males and 37.5% were females. We observed male predominance (male-to-female ratio 1.6:1) that is

similar to other studies with the proportion of males ranging from 56.3% to 60.9%.22-25

Table 3: Laboratory parameters and illness severity scores of survivors and non-survivors

Laboratory parameters	Total patients (n=96)	Survivors (n=40)	Non-survivors (n=56)	p-value
	Median (Range)	Median (Range)	Median (Range)	
Hemoglobin (g/dL)	11.24 (4.8-17.1)	12.65 (7.6-17.1)	10.7 (4.8-17)	0.004
Hematocrit (%)	36.16 (17.28-58.68)	38.09 (19.18-58.68)	34.44 (17.28-55.6)	0.015
White blood cell count (thousand/mm^3)	11.3 (0.3-77.2)	9.9 (2.8-24.3)	12.07 (0.3-77.2)	0.154
Platelet count (lakhs/mm^3)	1.51 (0.003-5.80)	1.77 (3.8-4.14)	1.08 (0.06-5.80)	0.021
Random blood sugar (mg/dL)	139 (38-433)	154 (66-424)	121 (38-433)	0.850
Serum creatinine (mg/dL)	1.51 (0.35-10.52)	1.2 (0.52-10.51)	2.02 (0.35-10.52)	0.047
Serum sodium (mmol/L)	137 (118.7-163.8)	136.7 (118.7-144.9)	137 (119.9-163.8)	0.493
Serum potassium (mmol/L)	4.37 (2.68-8.34)	4.32 (2.71-7.26)	4.41 (2.68-8.34)	0.605
Serum total bilirubin (mg/dL)	0.8 (0.17-13.68)	0.73 (0.17-10.27)	0.94 (0.29-13.68)	0.020
Serum AST (IU/L)	63 (10-5439)	55.5 (15-1353)	74 (10-5439)	0.359
Serum ALT (IU/L)	43 (1-3839)	42 (5-699)	43.5 (1-3839)	0.710
Serum ALP (IU/L)	118.8 (40-1498)	104.5 (40-431)	124.5 (49-1498)	0.011
Serum albumin (g/dL)	2.99 (1.69-5.2)	3.17 (1.97-4.07)	2.65 (1.69-5.2)	< 0.001
Serum LDH (IU/L)	44.15 (179-11045)	416 (179-2103)	522.5 (211-11045)	0.065
D-Dimer (µg/mL)	3.72 (0-10)	2.12 (0-10)	4.51 (0-10)	0.011
Severity illness scores				
SOFA score*				
<8	52 (54.1)	29 (72.5)	23 (41.0)	0.004
>8	44 (45.8)	11 (27.5)	33 (58.9)	
APACHE score*				
<14	35 (36.4)	22 (55)	13 (23.2)	0.002
>14	61 (63.5)	18 (45)	43 (76.7)	

*Data represent number of patients (%); AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; SOFA: sequential organ failure assessment; APACHE: acute physiology and chronic health evaluation.

Many studies suggest that the male gender is more prone to non-recovery or mortality than the female gender among ARDS patients.26 However, we found no significant association between gender and the outcome of patients with ARDS. Our results are in agreement with the results of a study by Rashid et al.22 that no significant association existed between gender and the outcome of patients ($p = 0.074$).

The most common clinical manifestations in our patients were shortness of breath (55.2%), fever (39.5%), altered sensorium (23.9%), and cough (16.6%) while Rashid et al.22 reported that the most common clinical manifestations in patients with ARDS were fever (70.9%), shortness of breath (56.9%) and cough (45%). However, abdominal pain and altered sensorium were found in a higher number of non-survivors than survivors in our study.

Hypertension (32.2%) and type 2 diabetes mellitus (29.1%) were the most common comorbidities seen followed by COPD (15.6%) and CKD (10.4%) among our patients. In another study, the most common comorbidities were hypertension (25.2%), kidney disease (23.8%), and type 2 diabetes mellitus (22.3%), and were significantly associated with mortality which signifies that the presence of comorbidities is associated with greater risk of non-recovery among patients with ARDS.22 However, Sehgal et al.,23 Ando et al.,27 and Finney et al.28 found that there was no significant association between comorbidities and outcome which was consistent with our results of no significant association between comorbidities and outcome of patients with ARDS.

We observed that mean arterial pressure (MAP) was significantly lower among non-survivors than survivors (78.62 mmHg vs. 88.27 mmHg) and is similar to the observations by Balakrishnan et al.29 that MAP was significantly lower in the non-survivor group than the recovered group (61 mmHg vs. 67 mmHg).

Among our patients, vasopressors were needed in 32.5% of survivors and in 46.4% of non-survivors, but the association between the need for vasopressor support and outcome was statistically not significant. On the contrary, in the studies by Balakrishnan et al.29 and George et al.,30 the need for vasopressors was significantly higher among non-survivors than survivors and was associated with increased mortality. However, in a study done by Sharma et al.,24 vasopressor use was not significantly associated with mortality which is in agreement with our findings.

The majority of our patients had mild ARDS (43.7%) followed by moderate ARDS (39.5%) and severe ARDS (16.6%). In a study done by George et al.,30 the majority of patients had moderate ARDS (54.1%) followed by mild ARDS (39.3%) and severe ARDS (6.5%). In another study by Balakrishnan et al.,29 the majority of patients had severe ARDS (36%) followed by moderate ARDS (33%) and mild ARDS (31%).

The difference in the severity of ARDS in different studies may be due to differences in age and etiology of ARDS as per different geographical locations. George et al.30 observed that all patients with severe ARDS succumbed to illness while patients with moderate ARDS showed 42.5% mortality, and those with mild ARDS showed 16.6% mortality. The mortality was comparatively lower among our patients with severe ARDS (75%) and higher in patients with moderate ARDS (60.5%), and those with mild ARDS (50%). However, the association between severity of ARDS and mortality was not significant.

Laboratory parameters such as hemoglobin, platelet count, hematocrit, and serum albumin were significantly lower while serum creatinine, serum total bilirubin, ALP, and D-dimer were higher among non-survivors than survivors among our patients. Our findings are corroborated by findings of a study by Sharma et al.,24 that serum albumin was significantly lower and serum creatinine was significantly higher among non-survivors, while low hematocrit and high serum total bilirubin did not show a significant association with mortality. In the study by George et al.,30 serum creatinine was higher among non-survivors while low serum albumin and raised serum total bilirubin did not have a significant association with mortality. In another study by Sehgal et al.,23 low hemoglobin and low serum albumin levels were

not associated with mortality.

We observed that mechanical ventilation was required for 82.5% of survivors and 94.6% of non-survivors and the difference was statistically not significant. However, Rashid et al.22 found a significant difference between survivors and non-survivors regarding the need for mechanical ventilation which was associated with an increased risk of mortality.

In our patients, the severity of illness scores, such as SOFA and APACHE scores, were higher in the non-survivor group than the survivor group, and the association between the severity of illness scores and the outcome was found to be statistically significant, which is similar to the findings of studies done by Sharma et al.,24 Balakrishnan et al.,29 and George et al.30 that both SOFA and APACHE scores were significantly higher among non-survivors in comparison to survivors.

We noted that overall the most common cause of ARDS was sepsis (45.8%), followed by pneumonia (41.6%). However, in a study done by Sharma et al.,24 the most common cause of ARDS was pneumonia, followed by sepsis. In our patients, the most common cause of direct lung injury was pneumonia, while the most common cause of indirect lung injury was sepsis, which is similar to the findings of the study by George et al.30

The majority of our patients had a non-pulmonary cause of ARDS (55.2%), which is similar to the observations made by Balakrishnan et al.29 and Bhadade et al.31 that non-pulmonary causes of ARDS accounted for 69% and 75% of total patients of ARDS, respectively.

In the study done by Balakrishnan et al.,29 all patients with pulmonary ARDS succumbed to the disease, while out of 43 of our patients with pulmonary ARDS, only 32 patients (74.4%) succumbed to the disease. Rashid et al.22 observed that pneumonia and sepsis were significant predictors of mortality, which is similar to our findings that pneumonia and sepsis had a significant association with the outcome of patients with ARDS.

Mortality occurred in 58.3% of our patients with ARDS, which is similar to mortality rates of 56.2% and 52.5% observed by Sharma et al.24 and Rashid et al.22 However, Sehgal et al.23 and George et al.30 found lower mortality rates, which were 35.8% and 36%, respectively, while Balakrishnan et al.29 observed a higher mortality rate of 79% among patients with ARDS. The difference in mortality rates in various studies may be attributed to differences in the age of patients, duration, etiology, and severity of ARDS, and treatment facilities available at various centers.

Limitations of the study

This study has several limitations. As it was conducted at a single tertiary care center, the findings may not be generalizable to the diverse Indian population, where regional differences in healthcare access and disease burden exist. There may be a potential selection bias as inclusion of only patients admitted to a tertiary care hospital excluded those treated at primary or secondary levels. Long-term follow-up was not available, restricting conclusions to in-hospital outcomes. Despite these limitations, the study provides important insights into ARDS in the Indian context and underscores the need for larger multicenter studies with standardized protocols and extended follow-up.

Conclusions

Etiological factors such as pneumonia and sepsis were associated with an increased risk of mortality. Sepsis was overall the most common cause of ARDS while pneumonia was the most common direct cause of ARDS.

Abdominal pain, altered sensorium, and low mean arterial pressure (MAP) were associated with an increased risk of mortality. Anemia, low hematocrit, low platelet count, hypoalbuminemia, raised serum creatinine, hepatic involvement, and raised D-dimer were predictors of mortality in patients with ARDS. High illness severity scores such as APACHE and SOFA scores were associated with poor outcomes in patients with ARDS.

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Author contributions: RK, RMK, and RC conceptualized the study. ST and RC performed the clinical assessment. All authors analyzed and interpreted the data. ST drafted the manuscript. RK, RMK, and RC revised the manuscript for its intellectual content. All authors have read and approved the final manuscript

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Review Article

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Terminalia arjuna: An Ancient Cardioprotective Herb with Modern Clinical Relevance

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Cardiovascular illnesses continue to be the world's top cause of mortality, hence there is need of safe, reasonably priced and multi-target treatments. Long used as a cardiotonic in Ayurveda, Terminalia arjuna's rich phytochemistry has been associated to anti-inflammatory, lipid-lowering, vasodilatory, antioxidant, and inotropic properties. Small clinical trials indicate benefits in angina and heart failure, whereas preclinical research demonstrate beneficial lipid regulation, reduced infarct size, and enhanced cardiac function. But there aren't many large RCTs and different formulations, which limits the evidence. Its translational potential is highlighted by developments in network pharmacology, nano formulation, and AI-based modeling. The establishment of T. arjuna as an integrated cardioprotective phytopharmaceutical requires standardized extracts, molecular insights, and thorough multicentric studies.

Keywords: Terminalia arjuna, Arjuna (herb), Cardioprotection, Cardioprotective effects, Heart health, Phytochemicals.

Introduction

Cardiovascular diseases (CVDs) accounts for 19.8 million fatalities in 2022 becoming the world's largest cause of death amongst non-communicable diseases, with a disproportionately high burden on low- and middle-income nations. (1) Due to significant part of an aging population, demographic growth, and ongoing exposure to modifiable hazards, the number of deaths has increased even though worldwide age-standardized mortality rates have decreased as a result of advancements in prevention and treatment. The paradox—declining age-standardized rates but rising absolute deaths—reflects demographic transitions, with aging populations identified as the dominant driver of ischemic heart disease mortality worldwide. By 2027, an estimated 7.8 million premature CVD deaths are projected annually, with the steepest rise in low- and middle-income regions. This underscores the urgent need for innovative, affordable, and accessible cardioprotective therapies despite existing treatment advances. (2) Conventional pharmacotherapies (such as antiplatelets, statins, β-blockers, and ACE inhibitors) and surgical interventions have improved outcomes in ischemic heart disease and heart failure, but challenges such as high costs, side effects, poor adherence, and lack of myocardial regeneration still pose as a hindrance. (3) These gaps emphasize the need for sustainable and myocardium-targeted therapies. Plant-based cardioprotective agents have attracted considerable interest for their ability to act on multiple pathways involved in atherothrombosis, oxidative stress, endothelial dysfunction, and adverse cardiac remodelling. *Terminalia arjuna*, a massive evergreen tree, indigenous to Indian subcontinent, long have been used to treat angina, hypertension, and heart failure symptoms. (4) For centuries, *T. arjuna* has been described in Ayurvedic texts as a cardiac tonic, and modern studies attribute its cardioprotective effects to diverse phytochemicals—particularly triterpenoids, flavonoids, glycosides, and polyphenols—with antioxidant, anti-inflammatory, lipid-lowering, vasodilatory, and inotropic activities.

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(5) It is appropriate to connect classical knowledge with contemporary pharmacology. Though translation is hampered by varied preparations, variable dose, and a lack of high-quality randomized studies, T. arjuna provides a polypharmacological profile that is in line with complex CVD pathobiology.

Ethnopharmacological Background

Terminalia arjuna (family Combretaceae), has a well-established role in Indian medicine, particularly Ayurveda, where its preparation from the bark has been regarded as a cardiotonic and remains the most commonly used across the Indian subcontinent. Classical texts such as the Charaka Samhita, Sushruta Samhita, describe it as a remedy that is recommended for conditions resembling angina, heart failure, hypertension, and dyslipidaemia, often in the form of decoctions, powders, or medicated oils. (6) Beyond Ayurveda, T. arjuna is also integrated into Unani and Siddha medicine, valued for its cardioprotective effects. The widespread use of T. arjuna across different traditional systems shows its cross-cultural relevance and similarity to modern cardiovascular disease patterns. This long history of use offers a solid basis for current scientific research to confirm its benefits, standardize formulations, and identify the active compounds and mechanisms behind its cardioprotective effects. (7)

Phytochemistry of Terminalia arjuna

Terminalia arjuna's cardioprotective actions are attributed to multiple classes of secondary metabolites which are concentrated chiefly in the stem bark. The major bioactive groups include triterpenoids, flavonoids, glycosides, tannins and polyphenols.

Figure 1:https://greencoverinitiative.com/trees/terminalia-arjuna-arjuna-tree/

These constituents have been repeatedly identified by phytochemical surveys and reviews and form the backbone of mechanistic studies that show antioxidant, anti-inflammatory, lipid-modulating, and vasodilatory. (8) Triterpenoids such as arjunolic acid and arjunic acid, two oleanane-type triterpenoid saponins are frequently isolated from the bark, have been extensively studied for their pharmacological effects. Flavonoids such as arjunone, arjunolone, luteolin, and other related flavones and flavanols are reported to support reactive oxygen species (ROS) scavenging and endothelial protection. In addition, glycosides like arjunetin, together with high-molecular-weight tannins and polyphenols, contribute significantly to the herb's therapeutic potential. Different plant parts and extraction techniques have different phytochemical compositions. Stem bark is the most widely utilized ingredient in both traditional and clinical formulations because it is the richest source of triterpenoids, tannins, and many flavonoids. Although the polyphenols and flavonoids found in leaves and fruits overlap, they are frequently found in varying relative abundances and have fewer triterpenoid saponins. (9) Recent metabolomic investigations of fruit extracts and flowers have identified unique secondary metabolites that may have supplementary bioactivities. When making extracts for study or therapeutic purposes, these variations support part-specific standardization. (10) Comprehensive structure–activity relationship analyses are still scarce, despite the fact that a number of isolated compounds—particularly arjunolic acid—have undergone pharmacological profiling. Although systematic medicinal-chemistry efforts are limited, existing work indicates that the saponin glycosidic moiety and certain oxidation patterns on the oleanane scaffold influence antioxidant and membrane-interacting characteristics. This gap prevents the development of synthetic analogs based on T. arjuna scaffolds or rational optimization. Modern tools like LC–MS/MS and metabolomics, combined with bioinformatics, now allow comprehensive profiling of T. arjuna, linking its metabolites to specific targets and pathways. This integrated approach supports multi-target mechanism discovery and advances standardized, mechanism-driven phytopharmaceutical development. (11)

Mechanisms of Cardioprotective Action of Terminalia arjuna

The diverse range of phytochemicals present in T. arjuna provides cardioprotective activity by acting synergistically on the key pathways implicated in cardiovascular disease. T. arjuna's triterpenoids and

flavonoids have shown to effectively neutralize free radicals and restore glutathione and superoxide dismutase. Hence it results in protection of myocardial membranes from oxidative stress, a central factor in atherosclerosis. (12, 13) Extracts of T. arjuna have also shown to repress pro-inflammatory cytokines (TNF-α, IL-6) and inhibit the activation of the NF-κB pathway. By controlling inflammation, the herb helps to prevent endothelial dysfunction and harmful vascular remodelling, key drivers of heart disease progression. T. arjuna extract reduces atherogenic burden by lowering the levels of LDL and triglycerides and also supports vascular health. Studies suggest that T. arjuna improves heart muscle contraction by supporting calcium balance and stabilizing membranes. Arjunolic acid inhibits apoptosis pathways and protect the cardiomyocytes by stabilizing mitochondrial membranes and enhancing pro-survival signalling. T. arjuna promotes vascular relaxation by influencing nitric oxide pathways and calcium channels, helping regulate blood pressure and enhance coronary blood flow. In-silico studies show that T. arjuna compounds can act on multiple cardiac proteins such as β1-adrenergic receptors, ACE, HMG-CoA reductase, and Na^+/K^+-ATPase, supporting its role as a broad-spectrum cardioprotective herb suited to the complex nature of cardiovascular diseases. (14)

Preclinical and Clinical studies

Across the studies, the crude extract from T. arjuna or it's purified compounds (majorly arjunolic acid) have shown cardioprotective activities like - improved left ventricular function, reduced infract size, attenuation of oxidative stress and inflammation and favourable effects on lipid profiles. (15) For preclinical work animal models of ischemia–reperfusion, experimental myocardial infarction, heart failure, and hypertension have been utilized for testing the herb. Limited comparisons with conventional cardiac medications, inconsistent extract production and dosage guidelines, and the absence of long-term safety or chronic toxicity assessments required for clinical translation continue to limit preclinical research on T. arjuna. (16) Recent work explores nanoparticle-based formulations of T. arjuna, showing better bioavailability, sustained release, and stronger preclinical effects. However, these studies remain preliminary and need standardized comparisons and thorough safety evaluation. (17)

Clinical studies on Terminalia arjuna suggest it may help reduce angina episodes, and offer some benefit in heart failure, but effects on heart function and long-term outcomes remain unclear. Overall, the evidence is weak to moderate because most trials are small, employ various preparations and dosages, and have brief follow-up. There is a paucity of information regarding long-term safety and drug-herb interactions, however the herb seems safe in the short term with just minor adverse effects. Larger, carefully planned multicentre trials using standardized extracts are required to validate T. arjuna's significance in cardiovascular care, even though it may now be helpful as an adjuvant or preventive treatment. (18, 19)

Modern Advances & Translational Potential

Terminalia arjuna can be transformed from a traditional cure into reproducible, mechanism-driven phytopharmaceuticals with translational potential thanks to recent developments in formulation science, systems biology, and computational techniques. By encapsulating T. arjuna's extracts or isolated molecules like arjunolic acid in nano-formulations like lipid nanoparticles, PLGA carriers, and metal nanoparticles has shown to improve bioavailability, control release, and enhance cardioprotective effects in preclinical ischemia models. (20) Studies suggest that T. arjuna may work synergistically with standard drugs like statins, β-blockers, and ACE inhibitors, with early trials showing improved lipid profiles and angina relief when used in combination. (21) Systems biology analyses reveal its compounds act on multiple heart-related targets (AKT1, TNF, IL-6, MAPK14), supporting a multi-target mechanism. Additionally, in-silico and machine-learning studies predict that key compounds such as arjunolic acid and arjunone strongly bind to β1-adrenergic receptors and ACE, indicating potential benefits in heart failure and hypertension. (22) T. arjuna has promise for regenerative medicine because of its anti-inflammatory and antioxidant properties, which may increase stem-cell survival following cardiac damage. Ex-vivo research has demonstrated that preconditioned stem cells are more resilient. It is becoming a contemporary integrative cardioprotective drug in conjunction with developments in nanotechnology, adjunctive therapy, systems pharmacology, and AI-driven predictions; nonetheless, the majority of the evidence is still preclinical, necessitating standardized formulations and carefully planned clinical trials. (23, 24)

Future Perspectives

Future research should adopt a multi-omics strategy to map the pathways influenced by T. arjuna and

identify reliable biomarkers. Majorly priority should be given to develop standardized phytopharmaceutical formulations to ensure reproducibility. Instead of depending solely on symptomatic outcomes, clinical translation needs large, multicentric randomized controlled trials (RCTs) engineered to detect hard endpoints like hospitalization and mortality. To ensure safety in actual polypharmacy situations, it is equally crucial to systematically investigate drug–herb interactions, especially those involving statins, anticoagulants, antiplatelets, and ACE inhibitors. T. arjuna may reach its full potential and bridge the gap between traditional knowledge and current cardiovascular medicine if it were positioned as an evidence-based preventive therapy in addition to contemporary medicines. (25)

Conclusion

Terminalia arjuna is a potential ancient cardiotonic that is becoming more and more relevant in modern medicine. A wide range of cardioprotective properties, including as lipid-lowering, anti-inflammatory, antioxidant, and vasodilatory activities, are supported by its rich phytochemical profile. However, thoroughly planned randomized controlled trials, greater molecular insights, and standardized formulations are necessary for effective clinical translation. The potential for T. arjuna to transform from a traditional herbal remedy into a validated, widely used cardioprotective phytopharmaceutical lies in the integration of emerging technologies, such as network pharmacology for multi-target mapping, omics-based approaches for pathway discovery, and nanoformulation for enhanced bioavailability.

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Review Article

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Microglial Equilibrium in Brain Function and Dysfunction

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Microglia, the neuroimmune cells of the central nervous system (CNS), play a crucial role in brain development, health, and disease. Initially thought to be "resting," they're now known to be highly active, constantly monitoring the brain tissue with their ramified processes to detect small changes in electrical balance, communication between nerve cells, or cell health. Through this constant vigilance, microglia control the removal of excess connections between nerve cells, fine-tune the brain's connections, provide nutrients and energy to cells, and coordinate the body's response to injury or infection. Their interactions with nerve cells, astrocytes, and oligodendrocytes further connect them to the larger network of brain cells that helps keep the brain in balance. However, when microglial regulation goes awry, these same functions can contribute to disease, including nerve cell loss, mental health disorders, brain injury, and autoimmune diseases. This review brings together the latest findings in microglial biology, focusing on their origins, surveillance methods, roles in nerve cell connections, metabolic control, and communication with other brain cells. Together, these insights show that microglia are both protectors of brain function and potential triggers of disease, putting them at the centre of brain health.

Keywords: Microglia; Neuroimmunology; Synaptic pruning; Brain homeostasis; Neurodegeneration

Introduction

Microglia are specialized immune cells that play a vital role in the CNS, making up 5–15% of all glial cells, depending on the brain region. Previously thought to be passive "resting" cells that only activate during injury or disease, microglia are now recognized as highly dynamic and adaptable, constantly monitoring their environment and adjusting their function in response to both physiological and pathological cues.

Microglia originate in the yolk sac from primitive erythromyeloid progenitors (EMPs) during early embryogenesis (Ginhoux et al., 2010; Kierdorf et al., 2013). These progenitors enter the developing brain before the blood–brain barrier forms, colonize the neuroepithelium around embryonic day 8.5 in mice (week 4 in humans), and multiply locally to establish a self-renewing population that lasts throughout life (Ginhoux and Prinz, 2015). Early environmental signals, including growth factors like TGF-β and IL-34, as well as neuronal activity, guide microglial maturation and the acquisition of homeostatic markers such as P2RY12, TMEM119, and CX3CR1, enabling their lifelong adaptation to the CNS niche (Butovsky et al., 2014).

Microglia lie at the center of neuroimmunology, serving as key mediators of communication between the immune and nervous systems. They respond to a wide range of signals, from pathogens and injury to normal neuronal activity, influencing processes such as synaptic plasticity, neurogenesis, and myelination. Dysregulated microglial responses contribute to neurodevelopmental, neuropsychiatric, and neurodegenerative disorders, highlighting their dual role as protectors of brain health and potential drivers of pathology.

This review focuses on the physiological functions of microglia, including their development, surveillance, synaptic refinement, trophic and metabolic support, regional specialization, interactions with other brain cells, and adaptive changes during aging.

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Microglial Surveillance, Synaptic Remodelling, and Crosstalk

Microglia are highly dynamic sentinels of the CNS, continuously extending and retracting their fine processes to survey the parenchyma. This vigilance, revealed through two-photon imaging, enables rapid detection of ionic changes, neurotransmitter shifts, or cellular injury. Neuronal "calm down" signals, including CX3CL1–CX3CR1 and CD200–CD200R pathways, restrain excessive microglial reactivity and preserve homeostasis (Diez et al., 2009). When cells become stressed or die, the release of ATP and UDP activates microglial purinergic receptors such as P2RY12, guiding microglial processes to the affected sites (Davalos et al., 2005). Beyond surveillance, microglia provide trophic and metabolic support by releasing factors such as BDNF and IGF-1, regulating adult neurogenesis, and phagocytosing debris and protein aggregates to prevent toxic buildup that contributes to age- and disease-related decline(Parkhurst et al., 2013).

Equally vital is their role in sculpting neural circuits. During development, microglia prune synapses in an activity-dependent manner, with complement proteins (C1q, C3) marking weak synapses for CR3-mediated engulfment (Schafer et al., 2012; Stephan et al., 2012). This refinement ensures efficient wiring of cognitive and sensory networks, while impaired pruning contributes to disorders such as autism and schizophrenia. Even in adulthood, microglia continue to remodel synapses in response to learning, stress, and experience, underscoring their lifelong role in circuit plasticity.

Microglial functions are further shaped by their diversity and interactions with surrounding cells. Single-cell transcriptomics reveals region-specific signatures reflecting local demands and vulnerabilities in disorders like Alzheimer's or Parkinson's disease. Crosstalk with other glia and neurons refines their responses while neuronal neurotransmitters and extracellular vesicles actively reprogram microglial states. Together, these surveillance, remodeling, and communication roles establish microglia as central coordinators of homeostasis, immunity, and plasticity in the CNS.

Microglia in Aging

As individuals age, microglial cells undergo significant changes in their physiology, marking a key transition point between their roles in maintaining homeostasis and triggering disease. In older microglia, altered morphology, reduced mobility, impaired surveillance, and decreased ability to clear debris, and synaptic remodelling contribute to age-related cognitive decline and an increased risk of neurodegenerative conditions (Spittau, 2017; Rim et al., 2024). At the molecular level, aging microglia experience shifts in gene expression, with increased activity of genes related to interferon response, oxidative stress, and antigen presentation. Simultaneously, there is a loss of key markers of homeostasis, such as P2RY12, TMEM119, and CX3CR1 (Hickman et al., 2013; Galatro et al., 2017). This results in a functional shift towards chronic, low-grade activation, which makes neurons more vulnerable to damage. However, aged microglia are not uniformly harmful; in some instances, they can still provide support and participate in repair, although with reduced effectiveness.

Researchers are exploring methods to rejuvenate or reset the function of aged microglia. Approaches under investigation include targeting the CSF1R protein to remove and replace aged microglia, reprogramming their metabolism, utilizing senolytic interventions to eliminate senescent cells, and modulating the communication between the immune system and the brain(Elmore et al., 2018). These efforts emphasize the flexibility of microglial cells and the potential to mitigate age-related dysfunctions that increase the risk of disease.

Microglial Heterogeneity and Pathological Roles

One of the most striking findings in recent years is the recognition that microglia are highly heterogeneous, varying across brain regions, developmental stages, and pathological contexts (Masuda et al., 2019, 2020). Early morphological observations hinted at this diversity, but advances in single-cell RNA sequencing and spatial transcriptomics have uncovered distinct transcriptional and functional states. In the healthy brain, homeostatic microglia express markers such as P2RY12, TMEM119, and TREM2, which help distinguish them from infiltrating macrophages (Butovsky et al., 2014). Under stress or disease, however, they transition into specialized subtypes.

A prominent example is disease-associated microglia (DAM), first described in Alzheimer's models, which downregulate homeostatic genes while upregulating phagocytic and lipid metabolism pathways, including Apoe, Trem2, and Tyrobp (Keren-Shaul et al., 2017). At the ultrastructural level, dark microglia emerge in states of chronic stress, aging, and neurodegeneration, exhibiting condensed cytoplasm, fragmented organelles, and enhanced synaptic engulfment, features consistent with hypervigilant or

stressed phenotypes (Bisht et al., 2016). Another recently described population, lipid-droplet–accumulating microglia (LDAM), arises in aging and neurodegeneration, characterized by impaired phagocytosis, elevated oxidative stress, and disrupted lipid metabolism (Marschallinger et al., 2020). Together, these examples underscore the remarkable plasticity of microglia and highlight the need for therapeutic approaches tailored to context- and state-specific functions.

Microglia in Neurological Disorders

Microglia play a key role in many brain diseases. In neurodegenerative disorders, they gather around amyloid-β plaques and tau tangles in Alzheimer's disease (AD), where they might remove aggregates through phagocytosis (Yuan et al., 2016). However, when activated chronically, they release cytokines and reactive oxygen species that cause synaptic loss. Genes linked to AD, such as TREM2, CD33, and CR1, are highly expressed in microglia, highlighting their importance. In Parkinson's disease, extracellular α-synuclein aggregates activate toll-like and inflammasome pathways, maintaining inflammation and oxidative stress; PET scans show increased microglial activity that correlates with disease severity. In amyotrophic lateral sclerosis and frontotemporal dementia, microglia initially support neurons but later turn proinflammatory, with mutations like C9orf72 impairing lysosomal function and increasing toxicity.

In traumatic and acquired CNS injuries, microglia quickly respond by clearing debris and releasing growth factors, but prolonged activation can damage the blood–brain barrier, cause swelling, and lead to long-term problems like post-traumatic epilepsy and dementia risk.

Finally, in psychiatric and neurodevelopmental disorders, microglia are involved in mood and cognitive issues. Chronic stress increases their inflammatory activity in depression, with antidepressants partly working through immune modulation. Excessive synaptic pruning in schizophrenia, influenced by C4 gene variants, leads to synapse loss. Maternal immune activation and changes in cytokine signaling link microglial dysfunction to autism spectrum disorder.

Advances in Microglial Biology and Therapeutic Frontiers

Over the past decade, research has completely changed our understanding of microglia. Initially seen as passive immune defenders, they're now recognized as key players in central nervous system health. Single-cell RNA sequencing, ATAC sequencing, and spatial transcriptomics have revealed that microglia exist along a spectrum of states, rather than fitting into distinct categories like resting or activated. For instance, in Alzheimer's disease, microglia take on disease-related traits marked by the loss of homeostatic molecules, such as P2RY12 and TMEM119. At the same time, they activate programs related to lipid metabolism and phagocytosis, influenced by genes like APOE and TREM2. These shifts are driven by epigenetic regulators, including PU.1, Sall1, and IRF8 for maintaining balance, and NF-kappa B and STATs for inflammatory reprogramming (Gosselin et al., 2017). Environmental stressors and systemic inflammation can also leave lasting imprints, modulating responses throughout the lifespan.

Recent advances in technology have led to unprecedented insights into in vivo processes. Two-photon microscopy has shown that microglia constantly extend and retract their processes to monitor brain tissue and respond quickly to threats. PET imaging using TSPO ligands has allowed researchers to visualize microglial activity in patients, while newer tracers like CSF1R and P2RY12 ligands offer greater precision (Garland et al., 2023). Genetic and chemogenetic approaches, including Cre driver lines and DREADDs, now enable researchers to manipulate microglial signaling in experiments. Additionally, human-induced pluripotent stem cell-derived microglia and brain organoid systems have provided personalized platforms for studying disease mutations and discovering new treatments.

A key focus has been immunometabolism. Depending on activation state, microglia shift between glycolysis and oxidative phosphorylation (Borst et al., 2019; Jung et al., 2025). Glycolysis supports quick inflammatory signaling, while fatty acid oxidation encourages repair and trophic support (Bernier et al., 2020). Disruption of lipid metabolism, such as with TREM2 mutations, can impair protective functions. Metabolites like succinate and NAD act as regulators of microglial activity and aging (Xie et al., 2020). These insights have guided therapeutic efforts with metabolic modulators such as metformin and PPAR gamma agonists, along with CSF1R inhibitors, TREM2 agonists, and inflammasome blockers. Complementary strategies include exercise, dietary changes, neurostimulation, and microbiome interventions.

Nevertheless, major challenges still exist. Microglial diversity across regions and disease stages

complicates therapy design. Current therapies often affect both microglia and peripheral macrophages, raising the need for central nervous system selective delivery. Biomarkers remain limited, with TSPO lacking specificity, although soluble TREM2 and multimodal ligand panels show promise. Looking forward, integration of multiomics, CRISPR functional screens, neuroimmuno engineering, and advanced organoid systems may enable patient-tailored strategies that preserve beneficial roles such as pruning and trophic support while suppressing maladaptive states. Ultimately, microglia must be understood as active regulators of lifelong brain health whose plasticity can be harnessed for resilience and repair.

Discussion

Microglia are now recognized as key players in maintaining the balance between neural health and disease. In normal physiology, they aid in synaptic refinement, trophic signaling, and tissue surveillance while constantly communicating with neurons, astrocytes, oligodendrocytes, endothelial cells, and peripheral immune signals. This ongoing interaction supports circuit stability and plasticity, placing microglia at the core of the neuroimmune network.

In pathology, however, microglia take on roles that can be both protective and harmful depending on timing and context. In neurodegenerative conditions such as Alzheimer's, Parkinson's, and frontotemporal dementia, they initially cluster around deposits and promote clearance, but prolonged activation increases oxidative stress and causes synaptic dysfunction. After trauma or ischemic stroke, their early functions include debris removal and supporting axonal regeneration, yet ongoing inflammatory signals can worsen secondary damage. In psychiatric and neurodevelopmental disorders, abnormal pruning and altered cytokine signaling interfere with circuit maturation, leading to long-term vulnerability. These varied outcomes are affected by genetic factors, age, sex, local cellular interactions, and systemic immune responses.

Therapeutic strategies, therefore, need careful calibration. Interventions that broadly suppress or activate microglia risk removing their essential protective functions. Current approaches aim to redirect microglial states instead of silencing them completely. This includes drugs like CSF1R inhibitors, inflammasome modulators, and TREM2 agonists, as well as complementary strategies such as lifestyle changes, neuromodulation, and microbiome-based therapies. The challenge is ensuring that treatments are specific to the context, controlled over time, and ideally tailored to the individual.

The emerging framework of precision neuroimmunology offers a path forward. Multiomics profiling, CRISPR functional analysis, humanized organoids, and computational models now allow detailed mapping of protective and pathogenic states. Incorporating variables such as aging, sex, and systemic immunity will be essential to determine therapeutic windows. Ultimately, the future of microglial therapy rests on preserving their indispensable functions while selectively mitigating their harmful contributions. Microglia should be viewed not only as contributors to pathology but also as potential allies in maintaining and restoring central nervous system health.

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